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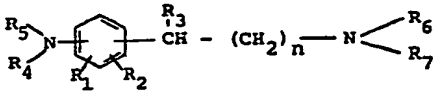
(54) Aminophenylalkylamine derivatives, a process for their preparation and their use as pharmaceuticals

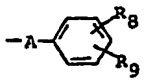
(57) Compounds of formula I



in which

R_1 represents hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,

R_2 represents hydrogen, halogen, C_1—C_4alkyl, C_1—C_4alkoxy or a group of formula



wherein

A represents oxygen, sulphur, carbonyl or a direct bond and

R_8 and R_9, independently, represent hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy

R_3 represents hydrogen or C_1—C_4alkyl,

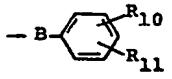
n is 0, 1 or 2,

R_4 represents C_4—C_{24}alkyl,

R_5 represents hydrogen, C_1—C_{24}alkyl or a group physiologically degradable to a hydrogen atom and

R_6 and R_7 represent, independently, hydrogen,

C_1—C_{24}alkyl, a group of formula



wherein

B represents C_1—C_6alkylene and

R_{10} and R_{11} represent, independently, hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy;

or a group physiologically degradable to a hydrogen atom; and the nitrogen containing groups are in meta- or para-position to each other and pharmaceutically acceptable acid addition salts thereof. The compounds are indicated for use in inhibiting hyperglycemia, for example in patients suffering from diabetes.

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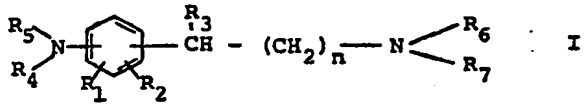
SPECIFICATION

4-amino-benzylamine derivatives, a process for their preparation and their use as pharmaceuticals.

This invention relates to novel 4-amino-benzylamine derivatives, their acid addition salts, a process for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as anit-hyperglycemic agents.

In particular the invention relates to pharmaceutical compositions comprising a compound of formula I

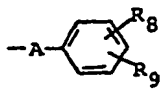


I

in which

R_1 represents hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,

R_2 represents hydrogen, halogen, C_1—C_4alkyl, C_1—C_4alkoxy or a group of formula



wherein

A represents oxygen, sulphur, carbonyl or a direct bond and

R_8 and R_9, independently, represent hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy

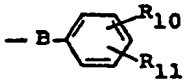
R_3 represents hydrogen or C_1—C_4alkyl,

n. is 0, 1 or 2,

R_4 represents C_4—C_{24}alkyl,

R_5 represents hydrogen, C_1—C_{24}alkyl or a group physiologically degradable to a hydrogen atom and

R_6 and R_7 represent, independently, hydrogen, C_1—C_{24}alkyl, a group of formula



wherein

B represents C_1—C_8alkylene and

R_{10} and R_{11} represent, independently, hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy;

or a group physiologically degradable to a hydrogen atom; and the nitrogen containing groups are in meta- or para-position to each other, or a pharmaceutically acceptable acid addition salt thereof, in admixture with a pharmaceutically acceptable carrier or diluent.

Halogen stands for fluorine, chlorine or bromine and alkyl moieties may be branched or unbranched.

The compounds of formula I possess pharmacological activity. In particular they are capable of inhibiting hyperglycemia especially post prandial hyperglycemia as indicated in oral starch loading tests.

These tests are carried out on Male Wistar rats (about 200 g in body weight, supplied by Royal-Hart Breeders, New York). The animals are fasted overnight (16 hours) before using. One hour after the oral administration of the vehicle (0.5% carboxymethyl cellulose (CMC) or water) — control or drug (12.5 to 200 mg/kg), the rats are given an oral starch load (2.5 g/kg of cooked wheat starch in 5% water). Thirty minutes after starch dosing, the rats are anesthetized by intraperitoneal injection of sodium hexobarbital (120 mg/kg). Blood is then obtained by cardiac puncture and collected in a test tube which contains 0.1 ml of heparin (1.000 units/ml). The heparinized blood is used to determine blood sugar level with an autoanalyzer. The percentage change in blood sugar is calculated by comparison of mean change in blood sugar after oral starch load (4 to 8 rats/treatment) with that of control group.

The compounds are thus indicated for use as anti-hyperglycemic agents in particular as agents for inhibition of post-prandial hyperglycemia especially in diabetic patients.

An indicated suitable daily dosage for the treatment of hyperglycemia (in particular post-prandial) is from about 200—3000 mg suitably administered in divided doses of 50—1500 mg two or four times daily or in retard form or particularly, in the case of post-prandial hyperglycemia three times a day at meal times.

The invention therefore also concerns a method of inhibiting hyperglycemia by administration of a compound of formula I, and also to compounds of formula I for use as pharmaceuticals e.g. as anti hyperglycemia agents in particular as agents for inhibiting post-prandial hyperglycemia or for use in the treatment of the human or animal body by therapy.

The compounds of formula IP may be administered in free base form or in the form of pharmaceutically acceptable acid addition salts such as the hydrochloride, which salt forms have the same order of activity as the free forms.

As indicated above, the compounds may also contain groups which are physiologically degradable to hydrogen atoms. Such groups may be any of the type known to leave (e.g. by hydrolysis) a tertiary amino moiety to form a secondary amino moiety, under conditions encountered in the gastrointestinal tract of a host and which form pharmaceutically acceptable derivatives. The leaving of such groups is caused, particularly in the stomach, by hydrolytic enzymes, such as esterases and amidases.

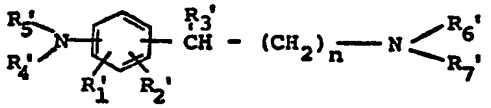
Representative of such groups are carboxymethyl, lower alkanoyl e.g. acetyl, succinyl, 1-(sodium sulpho) lower alkyl, 1-(sodium sulpho) polyhydroxalkyl and 1,3-bis(sodium sulpho)aralkyl; aryl being e.g. phenyl or naphthyl, and alkanoyl having from 2 to 6 carbon atoms. Such groups can be successively or simultaneously introduced in intermediate or end products in conventional manner whereby protection of reactive amino groups may be required for selective introduction.

The compounds of formula I or their pharmaceutically acceptable acid addition salts may be administered in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

The compound 4-(N-methylhexadecylamino)-benzylamine is known from GB Patent 1,004,281, but to our knowledge no useful pharmaceutical activity has been given for this compound.

The invention therefore further provides novel compounds within the scope of formula I above. Such compounds are those of formula Ip

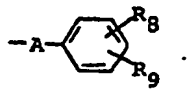


Ip

wherein

R_1' represents hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,

R_2' represents hydrogen, halogen, C_1—C_4alkyl, C_1—C_4alkoxy or a group of formula



wherein

A .. represents oxygen, sulphur, carbonyl or a direct bond and

R_8 and R_9, independently, represent hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,

R_3' represents hydrogen or C_1—C_4alkyl

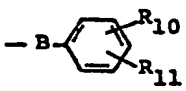
n is 0, 1 or 2,

R_4' represents C_4—C_{24}alkyl,

R_5' represents hydrogen, C_1—C_{24}alkyl or a group physiologically degradable to a hydrogen atom

and

R_6' and R_7' represent, independently, hydrogen, C_1—C_{24}alkyl, a group of formula



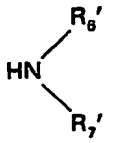
wherein

B represents C_1—C_8alkylene and

R_{10} and R_{11} represent, independently, hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy;

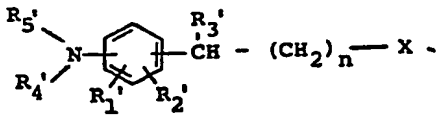
or a group physiologically degradable to a hydrogen atom, and the nitrogen containing groups are in meta- or para-position to each other with the proviso that when R_4' is hexadecyl, R_5' is methyl and n=0 at least one of R_1', R_2', R_3', R_6' and R_7' is other than hydrogen, or an acid addition salt thereof.

The compounds of formula Ip can be prepared according to the invention by reacting an amine of formula II



II

with a compound of formula III



III

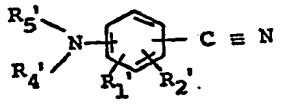
wherein

R_1' to R_7' and n are as defined above, and

X is a leaving group.

The reaction is carried out under conditions conventional for such reactions. Examples of leaving groups are halogen e.g. chlorine, bromine or iodine or alkyl or aryl sulphonyl groups e.g. tosyl.

Compounds of formula Ip wherein R_3', R_6' and R_7' represent hydrogen and n is 0 can alternatively be obtained according to the invention by reducing a compound of formula IV



IV

The reduction of a compound IV to its corresponding compound Ip may be carried out by means conventionally employed in reducing a nitrile function on an aromatic nucleus to its corresponding primary amine, e.g. by treatment with a metallo-hydride or catalytic hydrogenation; consideration being given to avoid alteration of any other ring substituents.

A convenient method of preparing a compound Ip is by treating a corresponding Compound IV with a metallo-hydride reducing agent such as an alkali metal aluminium hydride derivative e.g. $LiA1H_4$ under essentially anhydrous conditions, at moderate temperatures e.g. at from about 10° to 70°C, preferably at about 20° to 30°C, in an inert organic medium, e.g. a cyclic ether, such as tetrahydrofuran (THF).

Compounds of formula II and III are either known or may be prepared in conventional manner.

Compounds IV are either known from the literature e.g. Belgian Patent 870,687; Derwent Abstract 23,959B, or where not known may be prepared in a manner analogous to that disclosed in the literature for preparing the known compounds. For example, Compounds IV may be prepared by alkylation, i.e. by replacing one or, successively, two of the hydrogen atoms of the amino function, of a 4-aminobenzonitrile, using conventional procedures.

It will also be appreciated that compounds which contain primary amine groups can be converted e.g. by reductive amination followed optionally by introducton of a further alkyl group in conventional manner into the corresponding secondary and tertiary amine compounds.

The known compounds of Formula 1 may be prepared analogously.

The compounds of formula I (or Ip) may be isolated and purified using conventional techniques. They may be recovered in free base form or in the form of an acid addition salt. Free base forms and acid addition salt forms may be prepared or interconverted in conventional manner.

Examples of preferred substituents in compounds of formula I are

R_1 = a) CH_3
b) H

R_2 = H

R_3 = a) CH_3
b) H

n = a) 0
b) 1

R_4 = a) C_4—C_{24}alkyl
b) C_6—C_{20}alkyl
c) C_{12}—C_{18}alkyl

R_5 = a) H
b) C_1—C_4alkyl
c) C_4—C_{24}alkyl
d) C_8—C_{20}alkyl
e) C_{12}—C_{18}alkyl

R_6 = a) H
b) C_8—C_{20}alkyl

R_7 = a) H
b) C_8—C_{20}alkyl

Alkyl groups are preferably unbranched.
A preferred physiologically degradable group is C_1—C_4alkanoyl e.g. acetyl. When R_6 and/or R_7 represent a physiologically degradable group preferably only one of them at a time is alkanoyl.
The two nitrogen containing groups are preferably in para-position to each other.
Combinations of these preferred groups are of particular interest.
A particular group of compounds comprises those of formula Ip wherein
R_2' , R6' and R_7' represent hydrogen,
n is 0
R_4' is alkyl having 4 to 24 carbon atoms,
R_5' is hydrogen or a group physiologically degradable to a hydrogen atom.
Within this group compounds preferred compounds are those wherein
R_1' represents hydrogen and/or
R_4' is unbranched and has from 8 to 20 carbon atoms and/or
R_5' represents hydrogen.
The above listed preferred groups apply to compounds of formula I and where appropriate to those of formula Ip.
Two particularly interesting individual compounds are
4-hexadecylamino-benzylamine and
4-(N-methylhexadecylamino)-benzylamine.
The following examples are illustrative of the invention, temperatures are in degrees centigrade.

EXAMPLE 1
Preparation of 4-hexadecylaminobenzylamine (Cmpd. No. 1)
i) 4-Hexadecylaminobenzylbromide
To a solution of 3.47 g of 4-[N-n-hexadecylamino]-benzyl alcohol in 50 ml of dry tetrahydrofuran, are added (at 0°C), 5.26 g of triphenylphosphine and 6.66 g of tetrabromomethane. The reaction mixture is then stirrred at room temperature for 2 to 3 hours. Water is then added to the mixture, and the resulting mixture extracted five times with methylene chloride. The methylene chloride extracts are combined and washed twice with water, then dried over anhydrous sodium sulfate, and filtered, and the filtrate evaporated to dryness to obtain a residue. The residue is then flash-chromatographed from methylene chloride to obtain 4-hexadecylaminobenzylbromide.

ii) 4-Hexadecylaminobenzylamine
To a solution of 100 ml of ammonia saturated-methanol (containing about 3.4 g of ammonia) is added (dropwise) a solution of 4.10 g of 4-hexadecylaminobenzylbromide, and the reaction mixture stirred at room temperature for from 18 to 24 hours. Solvent is then removed by evaporation under vacuum, to obtain crude product. The product of this example is refined by rapid filtration of a methylene chloride solution over silica gel (m.p. 67—70°).

EXAMPLE 2
Preparation of 4-hexadecylaminobenzylamine (Compound No. 1)
(i) 4-hexadecylaminobenzonitrile
To a two liter 4-neck round bottom flask, equipped with mechanical stirrer, addition funnel and nitrogen gas inlet tube, are added 21.0 g (0.43 mole) of 50% sodium hydride in 600 ml of dimethylacetamide (DMA) and thereafter dropwise a solution of 50 g (0.42 mole) of 4-amino benzonitrile in 200 ml of DMA. After the reaction mixture has been stirred at room temperature for 0.5 hr., a solution of 129.2 g (0.42 mole) of 1-bromohexadecane in 300 ml of DMA is added dropwise, and the reaction mixture allowed to stir at room temperature for a further 16 hrs. The reaction mixture is then poured into water, the precipitate filtered off and air dried. The air-dried solid material is taken up in methylene chloride, dried over anhydrous sodium sulphate, filtered and the solvent removed under vacuum. Yielding a tan waxy solid, which upon recrystallization from hexane gives refined 4-hexadecylaminobenzonitrile m.p. 60—61.5°.

(ii) 4-hexadecylamino-benzylamine
A 2 liter 4 neck round bottom flask, equipped with addition funnel, reflux condenser and

mechanical stirrer is charged with 12.0 g (0.31 mole) of 1 lithium aluminium hydride and 1 liter THF. Then is added a solution of 55 g (0.16 mole) of p-hexadecylaminobenzonitrile in 500 ml THF dropwise with continual stirring. The reaction mixture is then refluxed for 5 hours and stirred at room temperature for 16 hrs. further. The reaction mixture is then decomposed by addition of 400 ml sat. aqueous sodium sulphate and extracted several times with ether. The combined ether extracts are washed with water, sat. brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under vacuum to obtain a residue (crude title product) which upon crystallization with acetonitrile gives refined title product, m.p. 67—70°.

Analogously to Example 1 or 2 as appropriate or as otherwise hereinbefore described, and employing appropriate starting materials, the following compounds of formula I may be obtained.

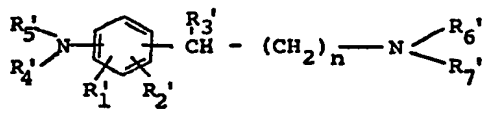
TABLE I

(nitrogen containing groups in para-position to each other $(R_4)(R_5)N$- in 4-position)

Cmpd. No.	R_1	R_2	R_3	n	R_4	R_5	R_6	R_7	Phys. Data m.p.
2	H	H	H	O	$n.C_{12}H_{25}$	H	H	H	
3	H	H	H	O	$n.C_{10}H_{21}$	H	H	H	
4	H	H	H	O	$n.C_{18}H_{37}$	H	H	H	
5	H	H	H	O	$(CH_3)_3CC_{10}H_{21}$	H	H	H	
6	3-Cl	H	H	O	$n.C_{16}H_{33}$	H	H	H	
7	$2\text{-}CH_3$	H	H	O	$n.C_{16}H_{33}$	H	H	H	
8	$2\text{-}CH_3O$	H	H	O	$n.C_{16}H_{33}$	H	H	H	
9	H	H	H	O	$n.C_{16}H_{33}$	CH_3	H	H	35—36°
10	H	H	H	O	$n.C_{16}H_{33}$	CH_3	$-\overset{O}{\overset{\|}{C}}-CH_3$	H	71.5—73°
11	H	H	H	O	$n.C_{16}H_{33}$	$n.C_{16}H_{33}$	H	H	36—38°
12	H	H	H	O	$n.C_{16}H_{33}$	$n.C_{16}H_{33}$	$-\overset{O}{\overset{\|}{C}}-CH_3$	H	59.6—61°

CLAIMS

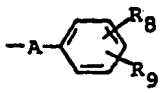
1. A compound of formula Ip



Ip

wherein

a) R_1' represents hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,
R_2' represents hydrogen, halogen, C_1—C_4alkyl, C_1—C_4alkoxy or a group of formula



wherein

A represents oxygen, sulphur, carbonyl or a direct bond and

R_8 and R_9, independently, represent hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,

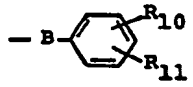
R_3' represents hydrogen or C_1—C_4alkyl,

n is 0, 1 or 2,

R_4' represents C_4—C_{24}alkyl,

R_5' represents hydrogen, C_1—C_{24}alkyl or a group physiologically degradable to a hydrogen atom and

R_6' and R_7' represent, independently, hydrogen, C_1—C_{24}alkyl, a group of formula



wherein B represents C_1—C_6alkylene and

R_{10} and R_{11} represent, independently, hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy;

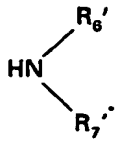
or a group physiologically degradable to a hydrogen atom, and the nitrogen containing groups are in meta- or para-position to each other with the proviso that when R_4' is hexadecyl, R_5' is methyl and n=0 at least one of R_1', R_2', R_3', R_8' and R_7' is other than hydrogen, or an acid addition salt thereof.

2. A compound as claimed in Claim 1 wherein R_2', R_3', R_6' and R_7' represent hydrogen n is 0, R_4' is alkyl having 4 to 24 carbon atoms, R_5' is hydrogen or a group physiologically degradable to a hydrogen atom.

3. A compound as claimed in Claim 2 wherein R_1' represents hydrogen and/or R_4' is unbranched and has from 8 to 20 carbon atoms and/or R_5' represents hydrogen.

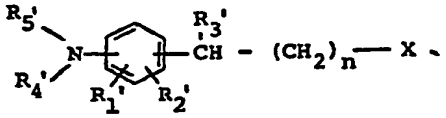
4. 4-Hexadecylaminobenzylamine.

5. A process for preparing a compound as claimed in Claim 1 which comprises reacting an amine of formula II



II

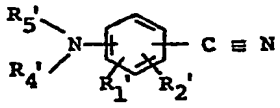
with a compound of formula III



III

wherein R_1' to R_7' and n are as defined above,

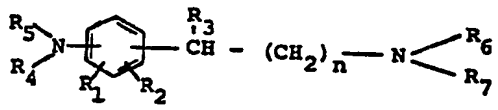
and X is a leaving group, or when R_3', R_6' and R_7' represent hydrogen and n is 0 reducing a compound of formula IV



IV

and recovering the compound thus obtained in free base form or in the form of an acid addition salt thereof.

6. Pharmaceutical compositions comprising a compound of formula I

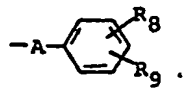


I

in which

R_1 represents hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy,

R_2 represents hydrogen, halogen, C_1—C_4alkyl, C_1—C_4alkoxy or a group of formula



wherein

A represents oxygen, sulphur, carbonyl or a direct bond and

R_8 and R_9, independently, represent hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy

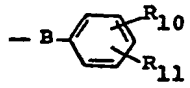
R_3 represents hydrogen or C_1—C_4alkyl,

n is 0, 1 or 2,

R_4 represents C_4—C_{24}alkyl,

R_5 represents hydrogen, C_1—C_{24}alkyl or a group physiologically degradable to a hydrogen atom and

R_6 and R_7 represent, independently, hydrogen, C_1—C_{24}alkyl, a group of formula



wherein

B represents C_1—C_6alkylene and R_{10} and

R_{11} represent, independently, hydrogen, halogen, C_1—C_4alkyl or C_1—C_4alkoxy;

or a group physiologically degradable to a hydrogen atom; and the nitrogen containing groups are in meta- or para-position to each other, or a pharmaceutically acceptable acid addition salt thereof, in admixture with a pharmaceutically acceptable carrier or diluent.

7. A method of inhibiting hyperglycemia which comprises administering to a subject in need of such treatment a compound as claimed in any one of Claims 1 to 3 or a composition as claimed in Claim 6.

8. A compound as claimed in any one of Claims 1 to 3 or a composition as claimed in Claim 6 for use as a pharmaceutical.

9. A compound as claimed in any one of Claims 1 to 3 or a composition as claimed in Claim 6 for use in inhibiting hyperglycemia, in particular post-prandial hyperglycemia.

10. A composition as claimed in Claim 5, a method as claimed in Claim 7 or a compound as claimed in Claim 7 wherein the compound employed is 4-hexadecylaminobenzylamine or 4-(N-methylhexadecylamino)-benzylamine.

11. The steps, features, compositions and compounds referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations or any two or more of said steps or features.

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